The Changing Lipidome during Cell Division

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Cell division entails dramatic membrane rearrangements, but what is the role of lipids in the process? Eggert et al. explore the dynamics of the lipidome during cell division and provide new insights on the functions of specific lipids in cytokinesis.

The division of the cytoplasm at the end of mitosis, termed cytokinesis, has been studied since the 19th century, with most efforts focusing on the contractile ring proteins and their regulators (Fededa and Gerlich, 2012). Until now, such studies have been overwhelmingly protein centric, with the few exceptions including important work on the roles of PI(4,5)P2, PI(3,4,5)P3, phosphatidylserine, and membrane rafts in cytokinesis (Field et al., 2005; Sagona et al., 2010; Dambournet et al., 2011, Ng et al., 2005; Echard, 2008; Echard, 2012). Here enters the Eggert group, who present in this issue the first comprehensive analysis of how the lipidome changes from interphase to cytokinesis (Atilla-Gokcumen et al., 2014).

The authors use state-of-the-art lipidomics technologies to demonstrate that the amounts of at least 11 specific lipids change both in time (interphase versus dividing) and in space (cell body versus midbody) (Figure 1). Of note, they identify changes of specific species within different lipid families—for instance, changes in the length and saturation of certain fatty acid chains and changes of lipids that represent a minor fraction of the total lipids. They also clearly demonstrate the importance of sphingolipids in cytokinesis, notably dihydroceramide, which is present at very low levels in interphase cells. Finally, this study points out how limited our current knowledge on lipids is by identifying unusual sterol derivative (hydroxy cholestane) and ether/ester-linked phosphatidic acids with no previous attributed biological functions.

Cells produce more than 10,000 different lipids using several hundred enzymes, and the roles of such a complexity in cellular processes are unclear. It is a tremendous challenge to specifically deplete a particular lipid of interest despite a century-long effort, as we often do not know the exact substrate specificity of enzymes involved in lipid generation and metabolism. In the present study, Eggert and colleagues employ a comprehensive RNA interference (RNAi) screen of 244 lipid-modifying enzymes, resulting in 23 hits that can cause cytokinesis failure (binucleate cells), half of which are involved in (glyco) sphingolipid metabolism. Of note, the authors demonstrated that the RNAi approach can induce compensatory reactions/nonpredictable feedbacks, which sometimes results in changes of nonexpected lipid species, making it difficult to directly connect cytokinesis failure to the depletion of a particular lipid. It is interesting that multifamily PI(4)P-5 kinase isoforms do not show up in the screen, though PI(4,5)P2 production is known to be essential for cytokinesis. Thus, the 23 targets identified from the screen are likely an underestimate.

Cell division results in significant mechanical stress accompanied by a change in tension of the plasma membrane due to the membrane-cytoskeleton interaction and a rise in the osmotic pressure (Stewart et al., 2011). Hinting at a mechanical role for lipids in cell division, Eggert and colleagues also take a reductionist approach by using atomic force microscopy (AFM) to analyze lipid films of total mixtures of lipids extracted from interphase versus dividing cells. Because it could be challenging to interpret such AFM measurements on lipid films, they complement this approach by measuring stiffness of whole cells after depletion of particular lipid-modifying enzymes. The findings that SMPD4/GALC/DGAT2 depletions all increase the F-actin level and that SMPD4 depletion increases the cell stiffness by 4-fold argue that lipids directly or indirectly influence cell mechanical properties. This opens new questions, such as how these lipids control actin levels, whether certain structural lipids increase membrane stiffness without changing the cytoskeleton, and whether there are large-scale domains of lipid phases during cell division. Hints of the existence of such domains come from a recent study revealing the insertion of discrete nonmembrane raft domains in the poles of dividing cells early in cytokinesis (Gudejko et al., 2012). Ideally, one wishes for means to functionally inhibit a particular lipid specie in an acute manner at a specific time in cell division. Practically, combined converging approaches are likely to be necessary for solving these complex biological questions as to the role of lipid species and domains in cellular processes.

Successful cytokinesis relies on a complex interplay among the plasma membrane, the underlying cytokeletons (actin and myosin, microtubule, septin, anillin, and ESCRT-III), and membrane-associated signaling molecules such as Rho or Src, as well as intracellular trafficking machinery. The current study only, so to speak, analyzes the lipidome changes at a whole-cell level. A potential

future direction would be to determine subcellular lipidome changes at the plasma membrane and on each intracellular compartment, in particular in specific endosomal subpathways, which play key roles in cytokinesis. Indeed, changes in specific intracellular compartments are likely to affect membrane trafficking and membrane tension. From this perspective, it is intriguing to note that their ceramide staining results indicate a vesicular localization of this lipid at midbodies. Local changes at the plasma membrane are likely to be critical. In some instances, though there may not be a significant change in the total cellular level of a specific lipid—for instance, PI(4,5)P2 measured in this study—such a lipid needs to be concentrated in the cytokinesis furrow (Field et al., 2005). Conversely, PI(4,5)P2 must be hydrolyzed from late cytokinesis bridges to ensure a successful abscission (Dambournet et al., 2011). For this well-studied lipid, an important feature is thus a dynamic and precisely regulated spatiotemporal subcellular distribution pattern, as opposed to a significant change of the lipid amount at a whole-cell level. Except for a few examples, such as PI(4,5)P2 and GM1, there is a cruel lack of reliable probes for detecting the dynamic localization and local changes of specific lipids during cell division. However, by interacting with lipid heads, these probes are likely to be selective for lipid subfamilies but not for a lipid specie with a particular acyl chain, which could be critical for its biological function, as highlighted in the present study. While the reported lipid composition of the midbody here is clearly an important first step, determining the local role of specific lipids at the subcellular level, though challenging, will be the essential next step for future work.

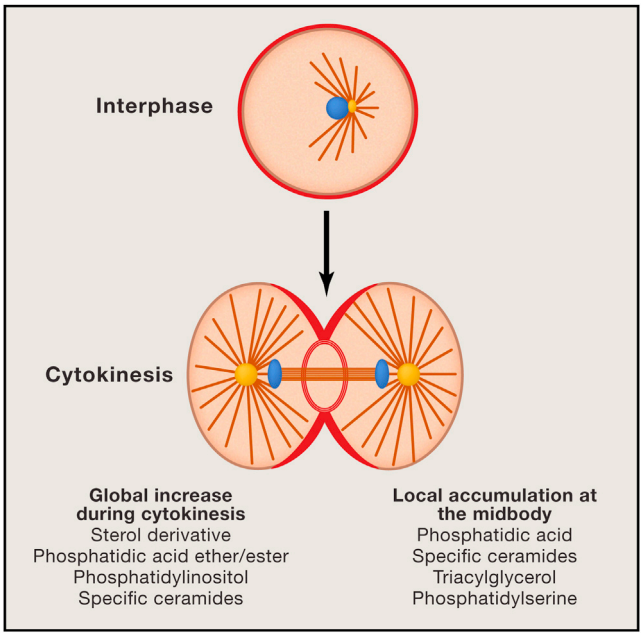

Figure 1. Lipid Species and Localization Changes during Cell Division

Eggert et al. show that, during cytokinesis, there are increases in the levels of specific lipids, whereas other lipids are accumulated later at the midbody. Key changes in lipid species are identified during cytokinesis.

REFERENCES

Atilla-Gokcumen, G.E., Muro, E., Relat-Goberna, J., Sasse, S., Bedigian, A., Coughlin, M.L., Garcia-Manyes, S., and Eggert, U.S. (2014). Cell *156*, this issue, 428–439.

Dambournet, D., Machicoane, M., Chesneau, L., Sachse, M., Rocancourt, M., El Marjou, A., Formstecher, E., Salomon, R., Goud, B., and Echard, A. (2011). Nat. Cell Biol. *13*, 981–988.

Echard, A. (2008). Biochem. Soc. Trans. *36*, 395–399.

Echard, A. (2012). Cytoskeleton (Hoboken) *69*, 893–912.

Fededa, J.P., and Gerlich, D.W. (2012). Nat. Cell Biol. *14*, 440–447.

Field, S.J., Madson, N., Kerr, M.L., Galbraith, K.A., Kennedy, C.E., Tahiliani, M., Wilkins, A., and Cantley, L.C. (2005). Curr. Biol. *15*, 1407–1412.

Gudejko, H.F., Alford, L.M., and Burgess, D.R. (2012). Cytoskeleton (Hoboken) *69*, 1000–1009.

Ng, M.M., Chang, F., and Burgess, D.R. (2005). Dev. Cell *9*, 781–790.

Sagona, A.P., Nezis, I.P., Pedersen, N.M., Liestøl, K., Poulton, J., Rusten, T.E., Skotheim, R.I., Raiborg, C., and Stenmark, H. (2010). Nat. Cell Biol. *12*, 362–371.

Stewart, M.P., Helenius, J., Toyoda, Y., Ramanathan, S.P., Muller, D.J., and Hyman, A.A. (2011). Nature *469*, 226–230.